COMBATTING FUTURE BIOLOGICAL THREATS – HOST-DIRECTED INTERVENTIONS TO EMERGING THREATS FOR RAPID RESPONSE

A Healthy Human Microbiome-informed Method For Enhancing In Silico Predictions Of Therapeutic Phage Safety

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Infections from multidrug-resistant (MDR) bacteria are a concern for warfighters who may acquire these infections in the field. Treatment of MDR bacterial infections has been challenging as the increase in antibiotic resistance outpaces development of new antibiotic treatments. An alternative avenue of therapeutics for these infections is the use of bacteriophages, viruses that infect specific host bacteria. Due to the narrow host range of these phages, which are often species or even strain-specific, a large set of diverse phages is necessary for phage therapy. It is critical to screen candidate phages for the presence of harmful or deleterious genes before these phages can be considered for use in humans. Our lab has been characterizing phage genomes using robust bioinformatics pipelines, ExempliPhi and Manual Annotation Studio; yet an average of 40-50% of phage proteins remain unannotated due to a lack of similarity with proteins of known functions in publicly available databases. To help combat this, we data-mined public microbiome and virome databases to create a database of phage proteins from healthy human microbiomes. Our hypothesis is that abundant phage proteins seen in healthy microbiomes will not be harmful when expressed by a therapeutic phage. Using this new database of phage proteins, we screen potential therapeutic phages in silico against these proteins, allowing for comparisons that don't rely on annotated functions being available. This provides us with an additional layer for the phage therapeutic safety assessment process, allowing for greater confidence in the phages that can be used to treat our warfighters. Additional future directions include using the created database as a training set for machine learning to further advance screening of possible therapeutic phages.

 The work at NMRC was supported by the Interservice Restoral Program and Navy WUN A1417.